Towards optimal decision making in personalized medicine

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Chapter 1

General introduction

1.1 PERSONALIZED MEDICINE

1.1.1 Definition

Personalized medicine, with its first use as the title of an article[1], has become a popular topic resulting in nearly 2,500 annual publications by 2012.[2] However, there is still no general agreed definition of personalized medicine as various terms can be used to describe its concept.[2,3] The definition is sometimes strictly given in the context of "genomic medicine", i.e., using genomic tests to select individual treatment eligibility and thus improve safety and patients' health outcomes via more efficient targeted risk stratification, and more tailored intervention.[2-5] The term "stratified medicine" can also be used to describe the concept of personalized medicine in which the subpopulations are not necessarily identified simply by their genomic information.[2,6] Personalized medicine is sometimes referred to as "individualized medicine"[3] to represent one end of a continuum of patient therapy to tailor the intervention at purely individual level rather than just at group level (i.e., one step further than stratified medicine).[7,8] Redekop and Mladsi[9] recently suggested a definition of personalized medicine in a broad perspective: "the use of the combined knowledge (genetic or otherwise) about a person to predict disease susceptibility, disease prognosis, or treatment response and thereby improve that person's health".

1.1.2 Towards better clinical decisions

Although the definition of personalized medicine differs among studies, one of the common core issues is to improve health through using risk-stratified treatment recommendations. Such recommendations suggest the allocation of different treatment regimens to individuals with different risks for outcomes.[10] Some major steps are taken into account to develop risk-stratified treatment recommendations.[11] First, different risk assessment tools (i.e., clinical risk prediction models) need to be applied to initially predict the likelihood of an underlying disease or disease-related outcomes over a given time period after incorporating patients' characteristics. Subsequently, the evidence about treatment effects on benefit and harm outcomes from randomized trials needs to be incorporated. Finally, a scientifically sound method is needed to investigate how the effects of different treatment regimens may vary across patients at different risks. This method should result in treatment thresholds defined with respect to patients' risk profiles that maximize the chance for benefits while minimizing

harms. Surprisingly, it has recently been shown in an environmental scan that only one of the clinical practice guidelines for the prevention or treatment of many common chronic diseases provides a clear explanation of how their treatment threshold was determined.[11] This suggests that taking into account the limited use that hitherto has been made of it, there is an enormous room for improvement and better return on investment.

1.1.3 Towards more efficient resource allocation

The emerging role of health economics and outcomes research in personalized medicine has recently been recognized, and is actively discussed.[12-16] It has been highlighted that the more important issue that needs to be tackled is not how personalized medicine can help target appropriate patients, but how this may maximize the net benefits for manufacturers, payers, and society at large.[2] Similar to the evaluation of other types of medical technologies, it is essential that such personalized approaches are able to ultimately cross the "fourth hurdle"[17-19] to secure their successful market registrations. Nowadays, very few specific guidelines exist to support the economic assessment of personalized medicine[20], which signals the necessity to develop innovative methods. The steps, as aforementioned to develop risk-stratified treatment recommendations, forms a clear framework to assess the clinical utility of personalized medicine. In a similar fashion, such a framework might also work and yield treatment thresholds after considering parameters that incorporate economic value of the comparative treatment regimens in the evaluation methods. Making better use of such evidence, patient care can be improved and more tailored and, more importantly, the use of the scarce health care resources can be optimized.

1.2 ROLE OF BIOMARKERS IN PERSONALIZED MEDICINE

1.2.1 state-of-the art

The complex underlying pathophysiologies of many diseases are as yet not fully understood. Biomarkers as indicators of the underlying molecular disease pathways may help to disentangle the riddles.[21-23] In theory, any substance that is objectively measured on or in a biological system can be used as a potential biomarker.[21,24] After biomarkers have been identified and properly validated during preclinical assays, it is necessary to investigate whether they have potential diagnostic or prognostic ability to indicate disease manifestation and/or progression and prognosis.[23] Furthermore, their additional ability in developing risk-stratified treatment recommendations compared to the personalized approach based on commonly used risk assessment tools is crucial when assessing the (potential) role of biomarkers in personalized medicine. To this end, rigorous steps need to be undertaken to critically evaluate the performance of biomarkers before they will eventually be adopted in clinical practice.[25,26] Readily available methods to support such evaluation have so far remained rather limited to abstract statistical terms, such as calibration (i.e., the goodness-of-fit between observed and predicted values), discrimination (i.e., the ability to separate cases from non-cases), and reclassification (i.e., the ability to correctly classify patients into a lower or higher risk category).[27,28] However, as stated in Hlatky et al.[25], the ultimate goal for biomarker research should not be to assess the added predictive value compared to standard risk markers, but to assess whether the use of such biomarkers can indeed change clinical outcomes in an affordable manner (i.e., cost-effectiveness) and satisfy the needs from multiple stakeholders (i.e., regulators, payers, patients etc.). Unfortunately, an agreed methodology to support the latter type of assessment is still lacking. This explains why the bench-to-bedside translations of both established and emerging biomarkers are still rare, despite the fact that the volume of literature devoted to biomarkers in clinical science is currently booming.[21,23]

The works presented in this thesis were performed within the framework of Center for Translational Molecular Medicine (CTMM). CTMM is a Dutch public-private partnership with one of the main aims to investigate the role of biomarkers in personalized medicine within different disease areas (i.e., cancer, cardiovascular diseases, infection and immunity, neurodegenerative diseases). Different partners within each project consortium collaborated to systematically evaluate the translational ability of biomarkers. After novel biomarkers have

been identified as promising based on evidence from preclinical assays, the research conducted in our group initially focused on using readily available methods to assess the biomarkers' clinical value. Subsequently, innovative methods were developed and introduced to evaluate the economic potential of such biomarkers to support their future clinical implementation.

1.2.2 Cost-effectiveness potential

To assess the long-term economic value (i.e., cost-effectiveness) of biomarkers, different types of state-transition models (STMs)[29,30] can be applied to perform comparative analyses after synthesizing appropriate evidence. A conventional approach may be used by the time a novel biomarker-based medical technology (i.e., biomarker test-kit) has been fully developed and the relevant evidence from clinical studies is available.[31] The results are intended to support reimbursement decision making by showing whether such technology can be implemented and adopted in daily clinical practice at affordable costs.[26,32] Nowadays, the evidence to support a conventional cost-effectiveness analysis of biomarkers is virtually always lacking. An important reason is that there is only a very limited number of studies specifically examining the clinical and economic value of laboratory tests.[33] Indeed little attention is paid to consider such tests as an inherent part of the overall treatment plan and thus a relevant target for potential costs or savings.

Increasingly, it is recommended that the cost-effectiveness evaluation should be performed already at an early stage, for instance, when only a prototype of the biomarker test-kit is available.[31,34] Notably, the conventional assessment does not allow incorporating the uncertainty encountered during the technology development phases into the analysis. As a consequence, it has long been considered difficult or even impossible to adequately inform the investment decision makers whether continuing such a costly process is worthwhile before it is too late. Early-stage STMs[26,35] are developed to support timely product investment decision making for its further development. The modeled outcome considered in this thesis is the commercial headroom available, which is defined as a price ceiling for which the intended clinical adoption of the novel technology may be deemed cost-effective.[36,37] Early-stage economic evaluation is characterized by evidence scarcity because the prototype of a novel technology (i.e., the biomarker test-kit) has hardly ever, if ever, been clinically applied.[34,35,38] Although the relevance of such assessment has been recognized, today most assessors lack

general understanding to quantify or qualify how the uncertainty caused by the limited evidence influences the future investment decision. This has thus far lead to very limited application to support the early-stage health economic decision making in biomarker research.

1.3 APPLICATIONS TO HEART FAILURE

The disease considered in this thesis is heart failure (HF). HF is a complex clinical syndrome which is characterized by symptoms such as breathlessness, fatigue, ankle swelling, and objective evidence of abnormal ventricular function.[39-43] It occurs when the heart muscle is weakened and enlarged thus preventing the heart from pumping normally and providing adequate blood flow for the body's needs. Worldwide, HF is one of the leading causes of death and disability.[44] The prevalence of HF is high.[39] In the U.S., there are more than 5.8 million adults who are suffering from HF, which accounts for approximately 2% of the total population.[40] The worldwide HF prevalence was estimated to be more than 26 million, and nearly 3.5 million new cases are diagnosed each year in Europe.[45] HF prevalence increases dramatically with age[46,47] and is rare under the age of 50. Importantly, HF is associated with a poor prognosis.[39] The 5-year mortality of HF was found to be 45-60% in the Framingham Heart Study.[41] In addition, morbidity is enormous with more than 1 million recorded HF-related hospitalizations annually.[42] The 6-month HF-related readmission rate is approximately 50%.[48] Worldwide the economic burden of HF is increasing at a stunning pace. The estimated direct and indirect HF health care costs exceeded $37 billion in 2009 in the U.S..[49] Total expenditure on HF ranges between 1% and 2% of the total health care budget in some other developed countries[50], of which around 75% is due to inpatient care.[51] Moreover, an increase in the prevalence and the corresponding cost burden of HF care is predicted for developed countries.[41] This trend is expected to continue until the middle of this century.[52]

In this thesis, we focus on circulating HF biomarkers that can be measured in the blood rather than the measurements that are routinely conducted as part of daily clinical practice (i.e., systolic and diastolic blood pressure).[21] The number of studies regarding the use of biomarkers in HF has increased spectacularly in the recent years.[22,53-56] Currently, the greatest impact of this type of research has been observed in the area of HF diagnosis, where the use of natriuretic peptides has gained widespread acceptance. A second main application of biomarkers in HF is the early identification of individuals at risk for adverse disease-related outcomes (i.e., prognosis). Finally, biomarkers in HF may also be intended to monitor how the disease is responding to a particular treatment regimen or to predict new-onset HF among healthy individuals.

1.4 OBJECTIVES AND THESIS OUTLINE

This thesis focuses on what methodological challenges to overcome to be able to show whether biomarkers have potential added value for personalized medicine towards optimal therapeutic and policy decision making using case studies in HF. To achieve this, several crucial steps need to be followed. Prior to the incorporation of biomarkers, the first part of this thesis **(chapters 2 and 3)** provides insights into the proof of concept of personalized HF care. Specifically, **chapter 2** describes the development of a risk prediction model to support early identification of healthy individuals at risk of both new onset HF with reduced and preserved ejection fraction (HFrEF and HFpEF). A treatment threshold is derived in **chapter 3** after investigating to what extent a risk-stratified allocation of HF disease management programs can improve clinical outcomes and reduce costs compared to a one-size-fits-all treatment strategy. Subsequent to the proof of the concept section, the second part of this thesis **(chapters 4 to 7)** systematically investigates whether it is worthwhile to further improve personalized HF care by incorporating biomarkers. **Chapter 4** investigates the clinical determinants and added prognostic value of a novel biomarker that has not been described previously in HF. **Chapter 5** serves as the methodological preparation for **chapter 7** in which an innovative model specification of a specific type of STM is introduced in the health economic setting. **Chapter 6** provides an application of the modeling technique introduced in **chapter 5** in a biomarker-based setting to evaluate the potential cost-effectiveness of biomarker-guided treatment response monitoring. **Chapter 7** evaluates the potential cost-effectiveness of a biomarker-based risk-stratified treatment recommendation compared to a treatment recommendation based on a risk prediction model which does not contain biomarkers. The treatment threshold determined from **chapter 3** and the modeling technique introduced in **chapter 5** are used to support the evaluation conducted in **chapter 7**. The main findings and implications of the various chapters, the methodological considerations, as well as the directions for future research are discussed in **chapter 8.**

1.5 REFERENCES

1. Gibson WM. Can personalized medicine survive? Can Fam Physician 1971;17(8):29-88.
2. O'Donnell JC. Personalized medicine and the role of health economics and outcomes research: issues, applications, emerging trends, and future research. Value Health 2013;16(6):S1-3.
3. Jain KK. Textbook of personalized medicine 2nd edition. New York: Springer; 2015.
4. Faulkner E, Annemans L, Garrison L, Helfand M, Holtorf A, Hornberger J, et al. Challenges in the development and reimbursement of personalized medicine-payer and manufacturer perspectives and implications for health economics and outcomes research: a report of the ISPOR personalized medicine special interest group. Value Health 2012;15(8):1162-71.
5. Hamburg MA, Collins FS. The path to personalized medicine. N Engl J Med 2010;363(4):301-4.
6. President's Council of Advisors on Science and Technology. Priorities for Personalized Medicine. Washington, DC: President's Council of Advisors on Science and Technology,2008.
7. Smith GD. Epidemiology, epigenetics and the 'Gloomy Prospect': embracing randomness in population health research and practice. Int J Epidemiol 2011;40(3):537-62.
8. Trusheim MR, Berndt ER, Douglas FL. Stratified medicine: strategic and economic implications of combining drugs and clinical biomarkers. Nat Rev Drug Discov 2007;6(4):287-93.
9. Redekop WK, Mladsi D. The faces of personalized medicine: a framework for understanding its meaning and scope. Value Health 2013;16(6):S4-9.
10. 27th Bethesda Conference. Matching the Intensity of Risk Factor Management with the Hazard for Coronary Disease Events. September 14-15, 1995. J Am Coll Cardiol 1996;27(5):957-1047.
11. Yu T, Vollenweider D, Varadhan R, Li T, Boyd C, Puhan MA. Support of personalized medicine through risk-stratified treatment recommendations - an environmental scan of clinical practice guidelines. BMC Med 2013;11:7.
12. Phillips KA, Sakowski JA, Trosman J, Douglas MP, Liang S, Neumann P. The economic value of personalized medicine tests: what we know and what we need to know. Genet Med 2014;16(3):251-7.
13. Jakka S, Rossbach M. An economic perspective on personalized medicine. Hugo J 2013;7:1.
14. Crawford JM, Aspinall MG. The business value and cost-effectiveness of genomic medicine. Pers Med 2012;9(3):265-86.
15. Postma MJ, Boersma C, Vandijck D, Vegter S, Le HH, Annemans L. Health technology assessments in personalized medicine: illustrations for cost-effectiveness analysis. Expert Rev Pharmacoecon Outcomes Res 2011;11(4):367-9.
16. Conti R, Veenstra DL, Armstrong K, Lesko LJ, Grosse SD. Personalized medicine and genomics: challenges and opportunities in assessing effectiveness, cost-effectiveness, and future research priorities. Med Decis Making 2010;30(3):328-40.
17. Rawlins MD. Crossing the fourth hurdle. Br J Clin Pharmacol 2012;73(6):855-60.
18. Rogowski WH. An economic theory of the fourth hurdle. Health Econ 2013;22(5):600-10.
19. Honig PK. Comparative effectiveness: the fourth hurdle in drug development and a role for clinical pharmacology. Clin Pharmacol Ther 2011;89(2):151-6.
20. Annemans L, Redekop K, Payne K. Current methodological issues in the economic assessment of personalized medicine. Value Health 2013;16(6):S20-6.

21. Ahmad T, Fiuzat M, Pencina MJ, Geller NL, Zannad F, Cleland JGF, et al. Charting a roadmap for heart failure biomarker studies. JACC Heart Fail 2014;2(5):477-88.
22. Giannessi D. Multimarker approach for heart failure management: perspectives and limitations. Pharmacol Res 2011;64(1):11-24.
23. Ptolemy AS, Rifai N. What is a biomarker? Research investments and lack of clinical integration necessitate a review of biomarker terminology and validation schema. Scand J Clin Lab Invest 2010;70(Suppl 242):6-14.
24. Atkinson A, Colburn W, DeGruttola V, DeMets D, Downing G, Hoth D, et al. Biomarkers and surrogate endpoints: preferred definitions and conceptual framework. Clin Pharmacol Ther 2001;69(3):89-95.
25. Hlatky MA, Greenland P, Arnett DK, Ballantyne CM, Criqui MH, Elkind MSV, et al. Criteria for evaluation of novel markers of cardiovascular risk: a scientific statement from the American Heart Association. Circulation 2009;119(17):2408-16.
26. Postmus D, de Graaf G, Hillege HL, Steyerberg EW, Buskens E. A method for the early health technology assessment of novel biomarker measurement in primary prevention programs. Stat Med 2012;31(23):2733-44.
27. Pencina MJ, D'Agostino RB, Sr., D'Agostino RB, Jr., Vasan RS. Evaluating the added predictive ability of a new marker: from area under the ROC curve to reclassification and beyond. Stat Med 2008;27(2):157-72.
28. Pencina MJ, D'Agostino RB, Sr., Steyerberg EW. Extensions of net reclassification improvement calculations to measure usefulness of new biomarkers. Stat Med 2011;30(1):11-21.
29. Siebert U, Alagoz O, Bayoumi AM, Jahn B, Owens DK, Cohen DJ, et al. State-Transition Modeling: A Report of the ISPOR-SMDM Modeling Good Research Practices Task Force-3. Value Health 2012;15(6):812-20.
30. Soares MO, Canto e Castro L. Continuous time simulation and discretized models for cost-effectiveness analysis. Pharmacoeconomics 2012;30(12):1101-17.
31. Ijzerman MJ, Steuten LMG. Early assessment of medical technologies to inform product development and market access: a review of methods and applications. Appl Health Econ Health Policy 2011;9(5):331-47.
32. Pietzsch JB, Pate-Cornell ME. Early technology assessment of new medical devices. Int J Technol Assess Health Care 2008;24(1):36-44.
33. Scott MG. When do new biomarkers make economic sense? Scand J Clin Lab Invest. Supplementum 2010;242:90-5.
34. Markiewicz K, van Til JA, IJzerman MJ. Medical devices early assessment methods: systematic literature review. Int J Technol Assess Health Care 2014;30(2):137-46.
35. Cao Q, Postmus D, Hillege HL, Buskens E. Probability elicitation to inform early health economic evaluations of new medical technologies: a case study in heart failure disease management. Value Health 2013;16(4):529-35.
36. Cosh E, Girling A, Lilford R, McAteer H, Young T. Investing in new medical technologies: a decision framework. J Commer Biotechnol 2007;13(4):263-71.
37. McAteer H, Cosh E, Freeman G, Pandit A, Wood P, Lilford R. Cost-effectiveness analysis at the development phase of a potential health technology: examples based on tissue engineering of bladder and urethra. J Tissue Eng Regen Med 2007;1(5):343-9.
38. Ballini L, Minozzi S, Negro A, Pirini G, Grilli R. A method for addressing research gaps in HTA, developed whilst evaluating robotic-assisted surgery: a proposal. Health Res Policy Syst 2010;8:27.
39. Krum H, Abraham W. Heart failure. Lancet 2009;373(9667):941-55.

40. Lloyd-Jones D, Adams RJ, Brown TM, Carnethon M, Dai S, De Simone G, et al. Heart disease and stroke statistics—2010 update: A report from the American Heart Association. Circulation 2010;121(7):e46–215.
41. Levy D, Kenchaiah S, Larson M, Benjamin E, Kupka M, Ho K, et al. Long-term trends in the incidence of and survival with heart failure. N Engl J Med 2002;347(18):1397-402.
42. Go AS, Mozaffarian D, Roger VL, Benjamin EJ, Berry JD, Borden WB, et al. Heart disease and stroke statistics–2013 update: A report from the American Heart Association. Circulation 2013;127(1):e6–245.
43. Yancy C, Jessup M, Bozkurt B, Butler J, Casey Jr. DE, Drazner MH, et al. 2013 ACCF/AHA guideline for the management of heart failure: A report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol 2013;62(16):e147-239.
44. Katz AM. The "modern" view of heart failure: how did we get here? Circ Heart Fail 2008;1(1):63-71.
45. Lopez-Sendon, J. The heart failure epidemic. Medicographia 2011;33:363-9.
46. Mosterd A, Hoes A, de Bruyne M, Deckers J, Linker D, Hofman A, et al. Prevalence of heart failure and left ventricular dysfunction in the general population - The Rotterdam Study. Eur Heart J 1999;20(6):447-55.
47. Mosterd A, Cost B, Hoes A, de Bruijne M, Deckers J, Hofman A, et al. The prognosis of heart failure in the general population - The Rotterdam Study. Eur Heart J 2001;22(15):1318-27.
48. Krumholz H, Chen Y, Wang Y, Vaccarino V, Radford M, Horwitz R. Predictors of readmission among elderly survivors of admission with heart failure. Am Heart J 2000;139(1):72-7.
49. Lloyd-Jones D, Adams R, Carnethon M, De Simone G, Ferguson TB, Flegal K, et al. Heart Disease and Stroke Statistics-2009 Update: A Report From the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Circulation 2009;119(3):e21-181.
50. Berry C, Murdoch D, McMurray J. Economics of chronic heart failure. Eur J Heart Fail 2001;3(3):283-91.
51. Nieminen M, Bohm M, Cowie M, Drexler H, Filippatos G, Jondeau G, et al. Executive summary of the guidelines on the diagnosis and treatment of acute heart failure. Eur Heart J 2005;26(4):384-416.
52. Schocken DD, Benjamin EJ, Fonarow GC, Krumholz HM, Levy D, Mensah GA, et al. Prevention of heart failure - A scientific statement from the American Heart Association councils on epidemiology and prevention, clinical cardiology, cardiovascular nursing, and high blood pressure research; Quality of care and outcomes research interdisciplinary working group; and functional genomics and translational biology interdisciplinary working group. Circulation 2008;117(19):2544-65.
53. Ahmad T, Fiuzat M, Felker GM, O'Connor C. Novel biomarkers in chronic heart failure. Nat Rev Cardiol 2012;9(6):347-59.
54. van Kimmenade RRJ, Januzzi JL, Jr. Emerging Biomarkers in Heart Failure. Clin Chem 2012;58(1):127-38.
55. Braunwald E. Biomarkers in heart failure. N Engl J Med 2008;358(20):2148-59.
56. de Boer RA, Daniels LB, Maisel AS, Januzzi JLJ. State of the art: newer biomarkers in heart failure. Eur J Heart Fail 2015;17(6):559-69.

PART I

DEVELOPMENT OF RISK-STRATIFIED TREATMENT RECOMMENDATIONS